PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	MASked-unconTrolled hypERtension management based on office BP or on ambulatory Blood Pressure measurement (MASTER) Study. A randomised controlled trial protocol
AUTHORS	Parati, Gianfranco; Agabiti Rosei, Enrico; Bakris, George; Bilo, Grzegorz; Branzi, Giovanna; Cecchi, Franco; Chrostowska, Marzena; De la Sierra, Alejandro; Domenech, Monica; Dorobantu, Maria; Faria, Thays; Huo, Yong; Jelaković, Bojan; Kahan, Thomas; Konradi, Alexandra; Laurent, Stéphane; li, nanfang; Madan, Kushal; Mancia, Guiseppe; McManus, Richard; Modesti, Pietro Amedeo; Ochoa, Juan Eugenio; Octavio, José Andrés; Omboni, Stefano; Palatini, Paolo; Park, Jeong Bae; Pellegrini, Dario; Perl, Sabine; Podoleanu, Cristian; Pucci, Giacomo; Redon, Josep; Renna, Nicolas; Rhee, Moo Yong; Rodilla, Enrique; Sanchez, Ramiro; Schmieder, Roland; Soranna, Davide; Stergiou, George; Stojanovic, Milos; Tsioufis, Costas; Valsecchi, Maria Grazia; Veglio, Franco; Waisman, Gabriel; Wang, Ji; Wijnmaalen, Paulina; Zambon, Antonella; Zanchetti, Alberto; Zhang, Yuqing

VERSION 1 – REVIEW

REVIEWER	Burnier Michel Service of Nephrology and Hypertension University Hospital Rue du Bugnon 17, 1011 Lausanne, Switzerland
REVIEW RETURNED	08-Jan-2018

GENERAL COMMENTS	The protocol presented by Parati et al try to answer an excellent question which is still unresolved in the field of hypertension. The methodology is clearly defined, precise and standardized. There is only one ethical aspect which is not discussed in this protocol: is it acceptable to follow patients with a normal office but elevated out-of-office BP for 5 years without adapting the treatment particularly if patients know they are hypertensive at home when they measure their BP ? Knowing that masked uncontrolled hypertension is associated with a higher risk of cardiovascular complications, this may be at the limit of the ethics. In addition, if these patients have a target organ damage (LVH or microalbuminuria), this can be even more controversial. In the ABPM group, patients will have very frequent ABPM measurements. Whether this will be acceptable by patients needs to be demonstrated. What drop out rate has been calculated considering this fact?

REVIEWER	Joji Ishikawa Tokyo Metropolitan Geriatric Hospital and Institute of Gerontology
REVIEW RETURNED	23-Jan-2018

GENERAL COMMENTS	Parati, G, et al. demonstrated a protocol paper to compare OBP-guided to ABP-guided antihypertensive therapy (AHT). Although ABP has a superior predictive value of hypertensive target organ damage than OBP, there were no data whether physicians should treat BP based on OBP or ABP. This study will provide important data in antihypertensive treatment. However, the reviewer had some comments regarding to the protocol of this MASTER Study. Major comment 1. In patients who have higher OBP than ABP (i.e. those who have sustained hypertension and white coat hypertensive effect), OBP-guided AHT can be beneficial for reducing hypertensive target organ damage. Therefore, the reviewer guess that only patients with masked uncontrolled BP will be enrolled into this study. The reduction of BP under AHT will be largely attributable to baseline BP levels, regardless of BP device. Authors should clearly mention in this protocol papers and in result papers in the future, the results of this study will apply only to patients with masked uncontrolled ABP. 2. In ABP-guided AHT group, at least one of 3 ABP data (daytime ABP, nighttime ABP and 24hr ABP) will be targeted in this protocol. If the investigators want to test the difference in BP devices, but not to test chronologic effect, the investigators may need to consider that ABP guided AHT group will be targeting only daytime ABP, because OBP is measured only in daytime. It is controversial whether ABP guided AHT targeting nighttime ABP is beneficial in comparison to that targeting daytime ABP; this may be an additional problem. Minor comments 1. How the investigator confirm that physicians will not consider OBP in ABP-guided AHT group, although they will take OBP reading? 2. Please clarify the percentage of dropout from the protocol in the ABP-guided AHT group. 3. In home BP monitoring, patients can use their own validated BP device. Can patients use wrist home BP device? 4. Is it enough time to wait for several minutes before OBP measurement?

REVIEWER	Sante D. Pierdomenico University "G. d'Annunzio", Chieti-Pescara
REVIEW RETURNED	24-Jan-2018

GENERAL COMMENTS	This is an interesting and well written protocol. This study could provide information to clarify whether management of hypertension based on out-of-office BP might be superior to management based on office BP only, in terms of prevention/regression of organ damage and prevention of cardiovascular events. I feel one point deserves discussion. Eligible patients will be randomized to one of the two study groups following the dynamic allocation method for balancing baseline covariates (specifically center, age, sex, presence of diabetes and baseline Office SBP). Masked uncontrolled hypertension (MUCH) will be defined as clinic BP<140/90 mmHg, and at least one (or more) of the following: 1) daytime BP≥135/85 mmHg (daytime MUCH); 2) nighttime BP≥120/70 mmHg (nighttime MUCH) and, 3) 24h BP ≥130/80 mmHg (24-h MUCH). Thus any MUCH will be included. However, patients with daytime MUCH could have higher 24-h BP

	(up to 10 mmHg) than those with nighttime MUCH. For example, a patient from our database had daytime BP 138/85 mmHg, nighttime BP 117/69 and 24-h BP 133/81 (daytime and 24-h MUCH), whereas another one had daytime BP 123/71, nighttime BP 120/71 and 24-h BP 122/71 (nighttime MUCH). A substantial difference between these two types of patients could persist even after daytime or nighttime BP values are reduced within the normal ranges. This aspect could have some influence on prevention or regression of organ damage and on prevention of cardiovascular events. I wonder whether Group 1 and 2 will be balanced for MUCH type or whether patients with daytime or nighttime or 24-h MUCH will be analyzed separately.

VERSION 1 – AUTHOR RESPONSE

REPLY TO REVIEWER COMMENTS
Reviewer 1
Reviewer Name: Burnier Michel
Institution and Country: Service of Nephrology and Hypertension, University Hospital, Rue du Bugnon 17, 1011 Lausanne Switzerland Please state any competing interests: None

Reviewer comment: The protocol presented by Parati et al try to answer an excellent question which is still unresolved in the field of hypertension. The methodology is clearly defined, precise and standardized.

Reply: We thank the Reviewer for the careful assessment of our paper and for his interest towards our work.

Reviewer comment: There is only one ethical aspect which is not discussed in this protocol: is it acceptable to follow patients with a normal office but elevated out-of-office BP for 5 years without adapting the treatment particularly if patients know they are hypertensive at home when they measure their BP ? Knowing that masked uncontrolled hypertension is associated with a higher risk of cardiovascular complications, this may be at the limit of the ethics. In addition, if these patients have a target organ damage (LVH or microalbuminuria), this can be even more controversial.

Reply: We thank the Reviewer for giving us the possibility to better clarify this issue. Indeed, up to date, there is no evidence from RCTs showing whether using ABPM or HBPM as a guide to antihypertensive treatment confers any benefit in terms of CV prevention. To our knowledge, the MASTER study is the first study so far addressing this important and still controversial issue. In fact, in absence of such an evidence, current hypertension guidelines provide some inconsistent recommendations in this regard (see as an example the ESH-ESC hypertension guidelines published in 2013). On one side, they still recommend OBP for guiding antihypertensive treatment, and OBP only is indicated in the guidelines cardiovascular risk matrix to assess the level of cardiovascular risk in individual subjects. On the other side, when addressing the issue of masked hypertension, they also mention the possibility of starting treatment in presence of an elevated cardiovascular risk level, although this is indicated as a possibility only, and this indication is based on “expert opinion” and not supported by any randomized trial result. Moreover, available ESH-ESC guidelines recommend use of ABPM and HBPM as a complement to OBP, by stating that “Out-of-office BP should be considered to confirm the diagnosis of hypertension, identify the type of hypertension, detect hypotensive episodes, and maximize prediction of CV risk” with a IIa class , level b evidence. Moreover they quite vaguely state that “. For out-of-office BP measurements, ABPM or HBPM may be considered depending on indication, availability, ease, cost of use and, if appropriate, patient preference, with a

IIb class level c evidence . It is thus clear that more evidence is needed to better support out-of-office BPM, and the MASTER study is specifically aimed at providing such evidence. No ethics committee of any of the centers participating in this study has in fact raised any ethical issue related to our study design. At any rate, we value the reviewer's comment and we have indeed since the beginning created a "Data and Safety Monitoring Board and an Events Adjudicating Committee" which will be constantly monitoring the study progress and will be monitoring the results of our study in terms of outcome and safety, with the possibility of stopping the study in case any major ethical issue might rise. Quite sincerely a large number of investigators participating in this study do believe that out-of-office BP should be used for hypertension management, but they at the same time cannot find any experimental support to their belief in the available trials. This is why they have committed themselves to explore this issue according to the rules of randomized intervention trials. Finally, concerning the reviewer's observation on HBPM influencing patients awareness, the study protocol has included measurement of home BP levels both in group 1 and group 2 but ONLY, at the screening visit, at 12 months and at the final visit of the study, in order not to add too much complications to the study designing that is focused on the comparison between OBP-based and ABP based hypertension management only, while HBP values will not be considered for taking treatment decisions, but will be used at study end for data analysis only .

Reviewer comment: In the ABPM group, patients will have very frequent ABPM measurements. Whether this will be acceptable by patients needs to be demonstrated. What drop-out rate has been calculated considering this fact?

Reply: In the ABPM group during the follow-up visits ABPM will be performed every 6 months, which is a reasonable compromise between what is recommended in clinical practice (i.e. 1 year) and the needs of our research. Please consider this will be done in the frame of a monitored study, in which, at variance from clinical practice, patients compliance with the procedure will be reinforced at each follow-up visit. Nonetheless, we have anticipated a dropout rate of 15% considering, among other factors, a possible patients' non- compliance with the study protocol requirements, including the need of repeated ABPMs.

Reviewer: 2
Reviewer Name: Joji Ishikawa
Institution and Country: Tokyo Metropolitan Geriatric Hospital and Institute of Gerontology Please state any competing interests: None

Reviewer comment: Parati, G, et al. demonstrated a protocol paper to compare OBP-guided to ABP-guided antihypertensive therapy (AHT). Although ABP has a superior predictive value of hypertensive target organ damage than OBP, there were no data whether physicians should treat BP based on OBP or ABP. This study will provide important data in antihypertensive treatment. However, the reviewer had some comments regarding to the protocol of this MASTER Study.

Reply: We thank the reviewer for the interest manifested towards our study Protocol, which is aimed indeed at answering the question on whether ABPM should be used to guide antihypertensive treatment in patients with masked uncontrolled hypertension.

Reviewer Major comment: In patients who have higher OBP than ABP (i.e. those who have sustained hypertension and white coat hypertensive effect), OBP-guided AHT can be beneficial for reducing hypertensive target organ damage. Therefore, the reviewer guess that only patients with masked uncontrolled BP will be enrolled into this study.

Reply: The reviewer is correct. Indeed, the main recruitment criterion for patients to be included in the MASTER study is the diagnosis of masked uncontrolled (on treatment) hypertension, defined as office

BP <140/90 mmHg, and one or more of the following situations: Ambulatory daytime BP ≥135/85 mmHg; Ambulatory night-time ABP ≥ 120/70 mmHg; Ambulatory 24h ABP ≥130/80 mmHg.

Reviewer Major comment: The reduction of BP under AHT will be largely attributable to baseline BP levels, regardless of BP device. Authors should clearly mention in this protocol papers and in result papers in the future, the results of this study will apply only to patients with masked uncontrolled ABP.

Reply: The reviewer is once more correct- Of course, the results of the present study will apply only to patients affected by MUCH (masked uncontrolled hypertension), who are characterized by controlled OBP and uncontrolled ambulatory systolic or diastolic BP values (24h or daytime or night-time).

Reviewer Major comment: In ABP-guided AHT group, at least one of 3 ABP data (daytime ABP, nighttime ABP and 24hr ABP) will be targeted in this protocol. If the investigators want to test the difference in BP devices, but not to test chronologic effect, the investigators may need to consider that ABP guided AHT group will be targeting only daytime ABP, because OBP is measured only in daytime. It is controversial whether ABP guided AHT targeting nighttime ABP is beneficial in comparison to that targeting daytime ABP; this may be an additional problem.

Reply: For defining MUCH we have considered the latest definition proposed by European Society of Hypertension practice guidelines for ambulatory blood pressure monitoring (Parati et al. Journal of Hypertension 2014, 32:1359–1366) according to which Masked uncontrolled hypertension in Treated individuals is defined as the presence of office BP <140/90 mmHg and any of the following conditions: 24-h ABP ≥130/80 mmHg and/or awake ABP ≥135/85 mmHg; and/or Sleep ABP ≥120/70 mmHg or Home BP ≥135/85 mmHg. In patients randomized to ABPM guided strategy, antihypertensive treatment will be intensified not only when SBP or DBP will exceed normal values during daytime (SBP ≥ 135 or DBP ≥85) but also in the case of ambulatory SBP or DBP elevation during nighttime (SBP ≥ 120 or DBP ≥70 mmHg) and/or the whole 24hr period (SBP ≥130 or DBP ≥ 80 mmHg). However, the MASTER study is not specifically addressing the value of an ABPM guided strategy for improving day-to-night BP profiles (i.e. it is not aimed at addressing the value of “chronotherapy”), but rather, more in general, to address whether improving achievement of BP control with an ABPM based hypertension management strategy is superior to an OBPM based strategy in changing LV mass and microalbuminuria (co-primary outcomes) at one year, in preventing CV events (secondary outcome) at 4 years, and in improving several BP-related variables throughout the study. As stated by the reviewer, there is still no evidence in patients affected by MUCH, on whether targeting nighttime ABP levels might be superior to targeting daytime ABP. Indeed, this might be an interesting question to be evaluated in future studies. Our study, with its sub analysis, will be in any case able to provide some information on this issue, by separately considering subjects with elevated daytime or night-time BP in presence of normal OBP levels.

Reviewer Minor comment: How the investigator confirm that physicians will not consider OBP in ABP-guided AHT group, although they will take OBP reading?

Reply: In the ABP-guided AHT group, both OBP and ABPM will be performed at each follow-up visit. However, modifications of antihypertensive treatment will be decided just on the basis of ABP values. The way physicians will modify treatment will be constantly monitored through centralized web-based study monitoring and any inappropriate treatment decision will be immediately notified to the investigators. In fact, to guarantee that modifications of AHT are based on ABP values only, in the ABPM group, there is a specific page in the study e-CRF, in which investigators have to indicate the reason for treatment modification. This information will be controlled by the data management team of the MASTER study trough regular queries and web-based data check.

Reviewer Minor comment: Please clarify the percentage of dropout from the protocol in the ABP-guided AHT group.

Reply: The sample of the study (n=1240 subjects, 620 subjects per randomization arm) was calculated anticipating a dropout rate of 15% considering, among other factors, patients' non, compliance with the tests of the study including ABPM.

Reviewer Minor comment: In home BP monitoring, patients can use their own validated BP device. Can patients use wrist home BP device?

Reply: As indicated within the paper, blood pressure levels in both study groups will be measured by three BP measurement techniques (office BP, home and 24-ABPM) following the recommendations issued by ESH/ESC hypertension guidelines and BP monitoring groups. For HBPM, patients can use any of the currently available validated devices. Although automated wrist monitors are popular among patients, because measurements are readily obtained without the need to remove clothing, current guidelines, do not recommend their use because of several problems (i.e. peripheral vasoconstriction, alteration in BP waveform in more distal sites of recording, a particularly relevant effect of limb position in relation to heart level on the measured BP values, and the degree of flexion and extension of wrist on the measured BP value), that may lead to important inaccuracies of measurement. Wrist devices may also be inherently less reliable because of the difficulties in producing an accurate algorithm to estimate systolic and diastolic BP as there are two arteries at wrist level contributing to the oscillometric signal. Thus, following guidelines' recommendations, the MASTER study will advise for HBPM, the use of monitors that measure BP in the upper arm (brachial artery) which have been shown to be the most reliable in both clinical practice and research.

Reviewer Minor comment: Is it enough time to wait for several minutes before OBP measurement?

Reply: Office Blood pressure levels will be measured following the recommendations issued by ESH/ESC hypertension guidelines which advice performing BP measurements after several minutes of rest and with the subject having abstained from smoking, strenuous exercise or caffeine intake in the period preceding the measurements.

Reviewer: 3
Reviewer Name: Sante D. Pierdomenico
Institution and Country: University "G. d'Annunzio", Chieti-Pescara

Reviewer comment: This is an interesting and well written protocol. This study could provide information to clarify whether management of hypertension based on out-of-office BP might be superior to management based on office BP only, in terms of prevention/regression of organ damage and prevention of cardiovascular events.

Reply: We thank the Reviewer for the time dedicated to assess our paper and for the important points of criticism raised to help us improving our work.

Reviewer comment: I feel one point deserves discussion. Eligible patients will be randomized to one of the two study groups following the dynamic allocation method for balancing baseline covariates (specifically center, age, sex, presence of diabetes and baseline Office SBP). Masked uncontrolled hypertension (MUCH) will be defined as clinic BP<140/90 mmHg, and at least one (or more) of the following: 1) daytime BP≥135/85 mmHg (daytime MUCH); 2) nighttime BP≥120/70 mmHg (nighttime MUCH) and, 3) 24h BP ≥130/80 mmHg (24-h MUCH). Thus any MUCH will be included. However, patients with daytime MUCH could have higher 24-h BP (up to 10 mmHg) than those with nighttime MUCH. For example, a patient from our database had daytime BP 138/85 mmHg, nighttime BP

117/69 and 24-h BP 133/81 (daytime and 24-h MUCH), whereas another one had daytime BP 123/71, nighttime BP 120/71 and 24-h BP 122/71 (nighttime MUCH). A substantial difference between these two types of patients could persist even after daytime or nighttime BP values are reduced within the normal ranges. This aspect could have some influence on prevention or regression of organ damage and on prevention of cardiovascular events. I wonder whether Group 1 and 2 will be balanced for MUCH type or whether patients with daytime or nighttime or 24-h MUCH will be analyzed separately.

Reply: To define the presence of MUCH during the enrolment phase, we have considered the latest definition proposed by the ESH/ESC practice guidelines for blood pressure monitoring (Parati et al. Journal of Hypertension 2014, 32:1359–1366) according to which MUCH is defined as the presence of office BP <140/90 mmHg and any of the following conditions: 24-h ABP ≥130/80 mmHg and/or awake ABP ≥135/85 mmHg; and/or Sleep ABP ≥120/70 mmHg or Home BP ≥135/85 mmHg. Although the issue addressed by the reviewer is of upmost importance, for practical reasons, we have not foreseen balancing the study groups according to the type of MUCH (i.e. according to the presence of daytime MUCH, nighttime MUCH or a combination of them). However, investigators are recommended to normalize any ABP value higher than the normalcy references, whenever they occur during 24 hours. This is now more clearly stated in the study protocol. At any rate, we will also take into account the reviewer's suggestion to properly interpret our findings by the time of the statistical analyses.

VERSION 2 – REVIEW

REVIEWER	Burnier Michel Service of Nephrology and Hypertension CHUV 1011 Lausanne, Switzerland
REVIEW RETURNED	26-Jun-2018

GENERAL COMMENTS	No specific comments

REVIEWER	Joji Ishikawa Department of Cardiology Tokyo Metropolitan Geriatiric Hospital and Institute of Gerontology
REVIEW RETURNED	16-Jun-2018

GENERAL COMMENTS	The authors revised the paper following to the comments from the reviewer. The reviewer had no further comment.

REVIEWER	Sante D. Pierdomenico, MD, Associate Professor of Internal Medicine University "Gabriele d'Annunzio" Chieti-Pescara, Chieti, Italy
REVIEW RETURNED	20-Jun-2018

GENERAL COMMENTS	I have no other comments.